**Customer No. 26874**
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| Appl. No. | : 10/731,465 | Confirmation No. 5274 |
| Applicants | : Whitsett, *et al* | |
| Filed | : December 9, 2003 | |
| Title | : METHODS OF DIAGNOSIS AND TREATMENT OF INTERSTITIAL LUNG DISEASE | |
| TC/A.U. | : 1632 | |
| Examiner | : Montanari, David A. | |
| | : | |
| Docket No. | : 0010872.0507287 | |
| Customer No. | : 26874 | |

**DECLARATION UNDER 37 CFR 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This declaration under 37 CFR Sec. 1.132 is supportive of the Amendment and Response filed herewith. I, Jeffrey A. Whitsett, declare and say:

1. That I am a citizen of the United States and that I am one of the co-inventors in the above-referenced patent application; that I am employed by Cincinnati Children's Medical Center, and I was and still am, engaged in a research program in the field of Neonatology, Perinatal and Pulmonary Biology;

2. That I am familiar with the above-identified patent application Ser. No. 10/731,465, that I have reviewed the November 5, 2007 Office Action in the above captioned case; and that I am familiar with the following patent: U.S. Patent 6,838,428 B2 (Whitsett).

3. That I am familiar with the research studies as evidenced by the following references:

a. rSP-D/a in Sheep: Ikegami, M., Carter, K., Bishop, K., Yadav, A., Masterjohn, E., Brondyk, W., Scheule, R.K. and Whitsett, J.A.: Intratracheal recombinant surfactant protein D prevents endotoxin shock in the newborn preterm lamb. Am. J. Respir. Crit. Care Med. 173:1342-1347, 2006. (PMID: 16556693)

b. rSP-D/a in Mice: Ikegami, M., Scoville, E.A., Grant, S., Korfhagen, T., Brondyk, W., Scheule, R.K. and Whitsett, J.A.: Surfactant protein-D and surfactant inhibit endotoxin-induced pulmonary inflammation. Chest 132:1447-1454, 2007. (PMID: 17925426)

c. Purified SP-B: Hokuto, I., Ikegami, M., Yoshida, M., Takeda, K., Akira, S., Perl, A-K.T., Hull, W.M., Wert, S.E. and Whitsett, J.A.: Stat-3 is required for pulmonary homeostasis during hyperoxia. J. Clin. Invest. 113:28-37, 2004. (PMID: 14702106)

4. That I have performed research studies as evidenced by the following methods:

a. Purified SP-C was co-administered with bacteria intratracheally; Replacement of SP-C to reconstitute macrophage function in vivo:

b. Sftpc-/- mice (PND12) were sedated by intraperitoneal injection of dilute xylazine/ketamine and suspended on a 60 degree incline board.

c. The tongue was extended and a 50 µl aliquot of either a synthetic phospholipid preparation (12.5 mg/ml DPPC:POPG, Avanti polar lipids) or the phospholipid preparation containing 2.5% purified human SP-C by weight (protein/lipid) was instilled. The mice were placed in a warming incubator and allowed to recover. This procedure was repeated on two consecutive days. The half-life of SP-C in the mouse lung was previously determined to be 28 hours. Macrophages were recovered by BAL. 24 hours after the last treatment with SP-C on PND14.

d. Macrophages were then plated at 4X105 cells per well and used for the fluorescent bead assay and FACS analysis as described. To determine whether the oral aspiration technique produced uniform delivery of the sample throughout the distal parenchyma, control mice were treated with the phospholipid preparation containing a visual marker dye (0.04% amido black). The lungs of dye treated control mice were removed two hours after aspiration and examined. The pattern of marker dye distribution was uniform throughout all lobes, indicating that the distribution of SP-C by aspiration effectively reached the distal parenchyma. No dye was visible in the digestive tract of SP-C-phospholipid:dye treated mice. (from Glasser et al., J. Immunol., in revision, 2008). It did not acutely kill bacteria. Thus, SP-C modifies inflammation.

5. That SP-C lipid mixtures have been delivered intratracheally to treat acute surfactant deficieny for treatment of RDS. (see Davis, A.J., Jobe, A.H., Häfner, D., Ikegami, M.

Lung function in premature lambs and rabbits treated with a recombinant SP-C surfactant. Am. J. Respir. Crit. Care Med. 157:553-559, 1998).

6. That Surfactant proteins (SP-D SP-C, and SP-B) have been delivered intratracheally in mice; sheep and rabbits, usualy mixed with carrier lipids to enhance spreading and delivery throughout the lung. Mixtures of SP-B and SP-C in lipid extracts of cow/pig lungs or surfactant isolated from lungs are routinely given for treatment of acute respiratory distress syndrome affecting pre-term infants. A standard therapy (see Jobe, A.H. Pulmonary surfactant therapy. N. Engl. J. Med. 1993 328:861-868, 1993).

7. The [I need to ask if you can supply information here] That the delivery of the SP-C proteins to the lungs would be expected to act as a treatment of airway hyperresponsiveness and/or airflow limitation associated with respiratory disease involving an inflammatory response in a subject because the protein is a surface acting agent(?) and does not need to be effective at systemic delivery through the lung cells as with many other treatments. The present treatment with SP-C is a nonspecific treatment that will work regardless of the underlying source of inflammation. [Can we say any more about this?]

8. That the above studies clearly show that SP-C formulations can be delivered by instillation or inhalation after aerosolization or as microparticles.

9. That the above research studies clearly show that the present invention, as previously amended and discussed, provide a demonstrating the link between SP-C protein and the treatment of airway hyperresponsiveness and/or airflow limitation associated with respiratory disease involving an inflammatory response in a subject. This information, along with previously submitted declarations (Glasser and Whitsett) detail the link between SP-C deficiency and disease as well as the feasibility of treatment.

10. That the information supplied provide sufficient guidance to the skilled artisan as to enable the treatment of airway hyperresponsiveness and/or airflow limitation associated with respiratory disease involving an inflammatory response because (a) successful delivery of SP-C to the lungs is show along with similar treatments by SP-B and SP-D and, hence, delivery of the protein to the surfaces of the interior of the lung is fully enabled; (b) the information supplied demonstrates that one skilled in the art would expect the present invention to work in any respiratory disease involving an inflammatory response due to the similar pathology and etiology shown in the therapies with SP-D and SP-B for acute diseases as tested in mice or sheep; and (c) the SP-C surfactant is shown to be deliverable in vivo using known formulations of protein or protein and lipid combinations. Therefore, the information and references provided herein by Applicant and the previously submitted Glasser and Whitsett declarations sufficiently teach the skilled artisan how to treat airway hyperresponsiveness and/or airflow limitation associated with respiratory disease involving an inflammatory response in a patient.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not.

Dr. Jeffrey A. Whitsett

5/4/08
Date

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